Docket No.: MCP-5017-USNP

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Buehler et al.	Conf. No.:	4561
Appln. No.:	10/674,702	Art Unit:	1627
Filed:	September 30, 2003	Examiner:	Layla Soroush

For: STABLE SUSPENSIONS FOR MEDICINAL DOSAGES

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August 10, 2010

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August 10, 2010
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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Dear Sir:

In response to the Office Action mailed May 12, 2010, the time for responding thereto being set to expire August 12, 2010, please consider the following amendment and remarks.

Listing of the Claims are reflected on page 2 of this paper.

Remarks begin on page 6 of this paper.

Claims

Please amend the claims as follows:

1. (Currently Amended) A pharmaceutical aqueous suspension comprising:

a) a therapeutically effective amount of suspended solid particles in crystal form comprising at least one active ingredient;

b) a thickener;

c) a uniformly dispersed nucleation inhibitor, wherein said nucleation inhibitor reduces growth rate of said active ingredient compared to suspensions not containing a nucleation inhibitor ~~and~~, wherein said nucleation inhibitor is polyvinylpyrrolidone, and wherein said nucleation inhibitor is present in an amount from above about 0 to about 5 % weight per volume; and

d) at least one amino polycarboxylic acid compound, wherein said amino polycarboxylic acid compound is present in an amount from about 0.005 to about 0.1 % weight per volume;

wherein the pharmaceutical aqueous suspension has a pH of about 3.7 to about 8; and

wherein the amino polycarboxylic acid compound imparts improved pH and viscosity stability to the pharmaceutical aqueous suspension.

2. (Previously Presented) A pharmaceutical aqueous suspension according to claim 1, wherein the suspended solid particles are hydrophobic and the suspension further comprises a surfactant.

3. (Previously Presented) A pharmaceutical aqueous suspension according to claim 1, wherein the suspended solid particles have a median particle size, as measured by laser scattering, of about 1 to about 20 microns.

4. (Previously Presented) A pharmaceutical aqueous suspension according to claim 1, wherein the thickener comprises a blend of at least a structuring agent and a swelling.

5. (Previously Presented) A pharmaceutical aqueous suspension according to claim 1, wherein the active ingredient is substantially insoluble in an aqueous environment at room temperature.

6. (Previously Presented) A pharmaceutical aqueous suspension according to claim 1, wherein the pharmaceutical aqueous suspension has a pH between about 3 and about 6 at room temperature.

7. (Canceled).

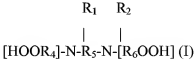
8. (Previously Presented) A pharmaceutical aqueous suspension according to claim 1, wherein the pH of the pharmaceutical aqueous suspension remains within about 0.2 pH units for a period of at least about four weeks when stored at a temperature of at least about 60°C.

9. (Previously Presented) A pharmaceutical aqueous suspension according to claim 1, wherein the viscosity remains constant for at least about two weeks when stored at a temperature of at least about 60°C.

10. (Previously Presented) A pharmaceutical aqueous suspension according to claim 1, wherein the viscosity remains within a range of plus or minus about 25% of its initial value for a period of at least about 8 weeks when stored at a temperature of about 60°C.

11. (Previously Presented) A pharmaceutical aqueous suspension according to claim 1, wherein the at least one amino polycarboxylic acid compound is a compound selected from the group consisting of:

formula (I) and pharmaceutically acceptable salts thereof:

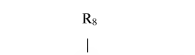


wherein R_1 and R_2, independently of one another, are hydrogen, hydroxy-terminated C_1-C_4 alkylene, carboxylic-terminated C_1-C_4 alkylene or N-$[R_3OOH]_m$;

wherein R_3, R_4, R_5 and R_6 independently of one another, are C_1-C_4 alkylene; and

wherein m is 1 or 2;

formula (II)



wherein R_7, R_8 and R_9, independently of one another, are hydrogen, C_1-C_4 alkyl, carboxylic-terminated C_1-C_4 alkylene or hydroxy-terminated C_1-C_4 alkylene; and

pharmaceutically acceptable salts of formula (I) or (II).

12. (Previously Presented) A pharmaceutical aqueous suspension according to claim 11, wherein the at least one amino polycarboxylic acid compound is represented by formula (I) and wherein R_1, R_2 and R_3 are ethylene.

13. (Previously Presented) A suspension according to claim 1, wherein the at least one amino polycarboxylic acid compound is selected from the group consisting of ethylenediaminetetraacetic acid (EDTA), hydroxyethylethylenediaminetriacetic acid, dihydroxyethylethylenediaminediacetic acid, 1,3-propanediaminetetraacetic acid, diethylenetriaminepentaacetic acid, triethylenetetraminehexaacetic acid, iminodiacetic acid, methyliminodiacetic acid, nitrilotriacetic acid, salts thereof, and mixtures thereof.

14. (Previously Presented) A suspension according to claim 1, wherein the at least one amino polycarboxylic acid compound is selected from ethylenediaminetetraacetic acid, salts thereof and mixtures thereof.

15. (Previously Presented) A suspension according to claim 1, wherein the amino polycarboxylic acid compound is disodium ethylenediaminetetraacetate.

16. (Previously Presented) A suspension according to claim 11, wherein the active ingredient is an anti-histamine or an analgesic.

17. (Previously Presented) A suspension according to claim 14, wherein the active ingredient is loratadine.

18. (Withdrawn) A suspension according to claim 16 wherein the active ingredient is acetaminophen or ibuprofen.

19. (Currently Amended) A pharmaceutical aqueous suspension comprising:

a) a therapeutically effective amount of suspended solid particles in crystal form

comprising at least one active ingredient;

b) a blended thickening component comprising xanthan gum and pre-gelatinized starch;

c) at least one amino polycarboxylic acid compound, wherein said amino polycarboxylic acid compound is present in an amount from about 0.005 to about 0.1 % weight per volume; and

d) polyvinylpyrrolidone wherein said polyvinylpyrrolidone is present in an amount from above about 0 to about 5 % weight per volume;

wherein the pharmaceutical aqueous suspension has a pH of about 3.7 to 8; and

wherein the amino polycarboxylic acid compound imparts improved pH and viscosity stability to the pharmaceutical aqueous suspension.

20. (Canceled).

21. (Previously Presented) A suspension according to claim 19, further comprising a surfactant.

22. (Canceled)..

23. (Previously Presented) A pharmaceutical aqueous suspension of claim 1, wherein said active ingredient is loratadine.

24. (Previously Presented) A pharmaceutical aqueous suspension of claim 19, wherein said active ingredient is loratadine.

25. (Previously Presented) A pharmaceutical aqueous suspension of claim 22, wherein said active ingredient is loratadine.

26. (New) The pharmaceutical aqueous suspension of claim 1, wherein said nucleation inhibitor is present in an amount from about 1 to about 3 % weight per volume.

26. (New) The pharmaceutical aqueous suspension of claim 1, wherein said amino polycarboxylic acid compound is present in an amount from about 0.01 to about 0.05 % weight per volume.

REMARKS

I. THE STATUS OF THE CLAIMS

Claims 1-6, 8-19, 21 and 23-25 are pending in the application. Claims 1-6, 8-17, 19, 21 and 23-25 are rejected. Claim 18 is withdrawn from consideration.

Claims 1 and 19 are amended; claim 22 is canceled; and claims 25 and 26 are added. Support for the amendment can be found in the specification at, for example, paragraph [0076] and paragraph [0083].

II. THE REJECTIONS UNDER 35 U.S.C. § 103

The Office Action rejects claims 1-6, 8-17, 19, 21-25 under 35 U.S.C. § 103 as being obvious over Gowan (U.S. Patent No. 5,374,659), Gergely et al. (U.S. Patent No. 5,834,019), Patel et al. (U.S. Patent No. 6,569,463), Eichman (U.S. Patent No. 5,980,882), McNamara et al. (U.S. Patent No. 6,423,298), Hagemann et al. (U.S. Patent No. 5,211,957) and Saeedi et al. (Prevention of Crystal Growth in Acetaminophen Suspensions by the Use of Polyvinyl Pyrrolidone Bovine Serum Albumin; DARU, Volume 11, Number 3 (2003)). In particular, the Office Action asserts:

> It would have been obvious to one of ordinary skill in the art to combine the teachings of Gowan, Jr., Gergely et al., Patel et al., Eichman and Hagemann et al. The motivation to combine the teachings is because (1) Gowan, Jr. teaches an aqueous pharmaceutical suspension composition comprising an insoluble pharmaceutical active, a suspension stabilizing effective amount of xanthan gum (hydrocolloid and thickener), pregelatinized starch (swelling agent and thickener) and polyoxyethylene sorbitan monooleate (surfactant) (see abstract). Application of the compositions and method of the present invention for medical and pharmaceutical uses can be accomplished by any clinical, medical and pharmaceutical methods and techniques as are presently or prospectively known to those skilled in the art. Thus it is intended that the present invention cover the modifications and variations of this invention provided that they come within the scope of the appended claims and their equivalents (col 7 lines 54-61); (2) Gergely et al. teaches [l]oratadine is virtually completely water-insoluble and has a very strongly hydrophobic character. It is thus extremely poorly wettable and therefore difficult to suspend. Its fine particles furthermore have the tendency to form a film on the water surface, to creep up the glass wall to a pronounced extent and to adhere relatively strongly there[;] (3) Patel et al.[,] teaches solubilizers for use in the compositions include triacetin, triethylcitrate, ethyloleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone (nucleation inhibitor) ([c]ol 29 line[s] 57-60). Other additives include enzyme inhibitors and chelating agents such as EDTA[;] (4) Eichman teaches drug resin complexes stabilized by chelating agents. "The particle size of a resin can differ between two resins." The chelating agent is preferably EDTA (amino polycarboxylic acid compound). EDTA is known to stabilize drugs in solution by retarding their oxidation [(]col 2 lines 60-61)[;] and (5) Hagemann et al. teaches [that] pharmaceutically

> acceptable excipients are, in particular[,] viscosity index improvers which are suitable for stabilizing aqueous suspensions and which inhibit sedimentation include PVP (col 4 lines 42-65). A skilled artisan would have reasonable expectation of effectively stabilizing loratidine (antihistamine) a water-insoluble pharmaceutical active.

Applicants respectfully traverse the rejection.

Applicants submit that in addition to the reasons provided in the Amendment filed on February 5, 2010, neither Gowan, Gergely et al., Patel et al., Eichman, nor Hagemann et al. disclose the use of **from above about 0 to about 5 % weight per volume polyvinylpyrrolidone** as a nucleation inhibitor ***and*** the use of **from about 0.005 to about 0.1 % weight per volume of an amino polycarboxylic acid compound to** impart improved pH and viscosity stability in a pharmaceutical composition.

In addition, newly cited McNamara et al., which discloses that EDTA may be employed as a stabilizer, and newly cited Saeedi et al., which discloses the use of polyvinylpyrrolidone and bovine serum albumin as crystal growth inhibitors of acetaminophen, also do not disclose or suggest the claimed invention. Reconsideration and withdrawal of the rejection of claims 1-6, 8-17, 19 and 21-25 under 35 U.S.C. § 103 over Gowan, Gergely et al., Patel et al., Eichman, McNamara et al., Hagemann et al. and Saeedi et al. are respectfully requested.

The Office Action rejects claims 1-6, 8-17, 19 and 21-25 under 35 U.S.C. § 103 as being obvious over Reinhardt et al. (U.S. Patent No. 6,217,998) in view of Hansenne et al. (U.S. Patent No. 6,916,464), Walch (U.S. Patent No. 6,790,847) and Patel et al. (U.S. Patent No. 6,569,463). In particular, the Office Action asserts:

> [A] skilled artisan would have a reasonable expectation of successfully producing a topical formulation with a local antihistamine effect with the pH claimed. The motivation comes from the teaching of Walch that the antihistamine loratadine is useful for topical application; the composition is incorporated with cosmetics inclusive of pigments; and Hansenne et al. [which discloses that] a pH which is compatable with the skin preferably ranging from 3 to 9 and better still from 3.5 to 7.5. Hence, a skilled artisan would have had reasonable expectation of successfully producing a composition with similar efficacy and results.

Applicants respectfully traverse the rejection.

Applicants submit that neither Reinhardt et al., which discloses a liquid makeup composition that is absorbed on and absorbent material and dried, Hansenne et al, which discloses sunscreen compositions, Walch, which discloses a drug composition containing loratadine and excipients, nor Patel et al., which was discussed previously, disclose the use of **from above about 0 to about 5 % weight per volume polyvinylpyrrolidone** as a nucleation inhibitor ***and*** the use of **from about 0.005 to about 0.1 % weight per volume of an amino polycarboxylic acid compound to** impart improved pH and viscosity stability **in a pharmaceutical composition.**

Reconsideration and withdrawal of the rejection of claims 1-6, 8-17 and 19, 21-25 under 35 U.S.C. § 103 over Reinhardt et al. in view of Hansenne et al., Walch and Patel et al. are respectfully requested.

III. Conclusion

Early consideration and prompt allowance of the claims are respectfully requested. If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 10-0750/MCP5017US/LAD.

Respectfully submitted,

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